Total Synthesis of the *Cephalotaxus* Alkaloids. A Problem in Nucleophilic Aromatic Substitution

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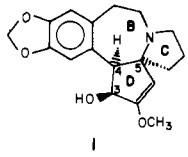
Abstract: The synthesis of cephalotaxine and cephalotaxinone has been achieved in 12–16% overall yield from pyrrolidone and 3,4-methylenedioxyphenylacetic acid. The strategy includes a key step which requires overall intramolecular nucleophilic aromatic substitution of an enolate anion onto an unactivated aromatic ring. Several methods give successful ring closure including addition to a transient aryne (15% yield), coupling via a σ-arylnickel complex (30%), and addition to a transient aryl radical generated from alkali metal reduction (45%) or from irradiation (94%).

Cephalotaxine (**1**) is the major constituent of the alkaloid fraction of the Japanese plum-yews, *Cephalotaxus drupacea* and *Cephalotaxus fortunei*. It was first isolated, and the structure was partially determined through the efforts of Paudler, Kerley, and McKay.[5] Less abundant in the same extracts is the harringtonine family of compounds (**2–5**), all rather simple esters of cephalotaxine. Standard assays performed by the Cancer Chemotherapy National Service Center showed that the harringtonines were active against lymphoid leukemia L-1210 and P-388 leukemia in mice.[6] This biological activity helped to stimulate a comprehensive program by the National Cancer Institute and the Department of Agriculture which resulted in detailed structural elucidation of cephalotaxine by X-ray diffraction analysis,[7,8] an extensive catalog of the minor alkaloid constituents from the *Cephalotaxus* including cephalotaxinone (**6**),[9] and detailed information on the antileukemia activity of the various components.[10]



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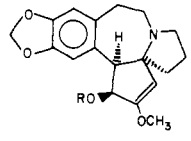
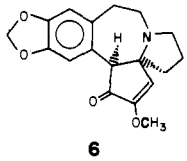


2: R = horringtonine



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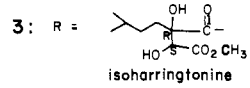

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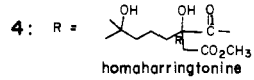
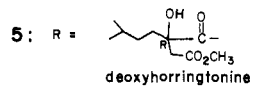


4: R = homoharringtonine

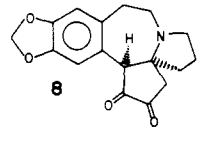


5: R = deoxyharringtonine

Cephalotaxine itself displays no significant antileukemia activity,[9] but it is an obvious intermediate in a total synthesis of the harringtonines (**2–5**). The unique spiro-fused five-membered rings annular to a benzazepine system appear to place the cephalotaxine skeleton in a class by itself.[11] These features attracted us to the problem of total synthesis of the *Cephalotaxus* alkaloids,[12,13] and we report here a convergent strategy which produces (+,−)-cephalotaxine in 13% yield overall from pyrrolidinone and 3,4-methylenedioxyphenylacetic acid.[14]

Strategy of the Synthesis. Cephalotaxine (**1**) has three contiguous chiral carbon atoms (C-3, C-4, and C-5 in **1**). Two important features of the structure simplify introduction of the proper configuration at C-3 and C-4 with respect to C-5. Metal hydride reduction of cephalotaxinone (**6**) is known to produce a single product, cephalotaxine, reflecting selectivity apparently due to the bowl-shaped arrangement of **6** (Figure 1).[15] At the same time, the carbonyl group in **6** is expected to activate the proton at C-4 toward acid- or base-catalyzed epimerization. No experimental evidence was available concerning the outcome of equilibration of the configuration at C-4, but inspection of molecular models supports the conclusion that the natural configuration (in **6**) is also the more stable arrangement. Therefore, cephalotaxinone (**6**) or 4-*epi*-cephalotaxinone (**7**) are the penultimate target structures.

Among the strategic disconnections available in dissecting the cephalotaxine skeleton, one pair produces a particularly useful simplification. Breaking of bonds a and b (Figure 2) leads to two fragments of similar complexity, the aromatic portion A and a spiroheterocycle B, which then become targets for two independent legs of a convergent synthetic plan. The spirocyclic structure B allows a further simplification in introduction of the α-methoxy-2-cyclopentenone portion (ring D in **6**). Methylation of a cyclopentane-1,2-dione precursor is an obvious tactic for preparation of this unit, but a question of regiospecificity arises if an unsymmetrical α-diketone such as **8** is involved.[16] However, the symmetry of a simpler intermediate such as **9** would eliminate the need for a regiospecific methylation.



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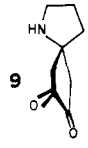
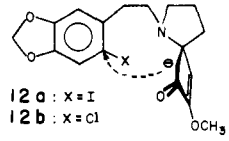


9

In implementing this strategy, bond a (Figure 2) can be formed directly through alkylation of spirocycle **10** with a properly functionalized benzene derivative (e.g., **11a** or **11b**). Several distinct pathways for closure of bond b are plausible; the most direct are likely to involve the stabilized anion **12,** proceeding via internal nucleophilic substitution



12a: X = I
12b: X = Cl

on the aryl ring. At the outset of this work, the known patterns of reactivity for nucleophilic aromatic substitution[17] did not allow optimism for success of such a pathway to **6.** The tactics for this ring closure, which constitute the central focus of this work, are discussed more fully below. The

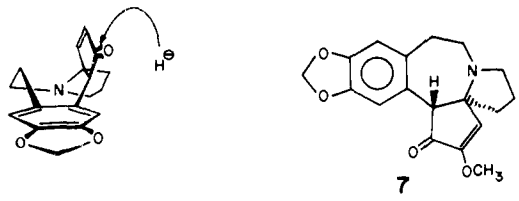


Figure 1. Selective hydride attack.

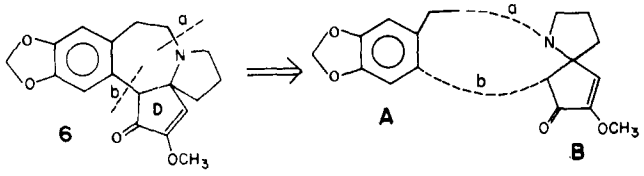
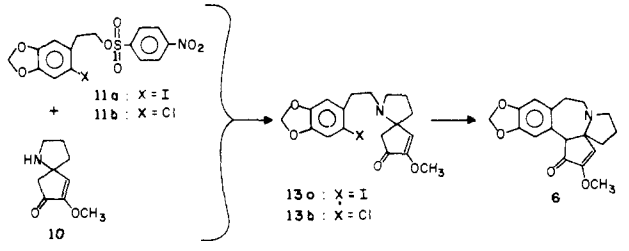


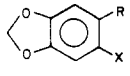
Figure 2. Strategic disconnections.

overall sequence, outlined in Scheme I, begins with the preparation of intermediates **10** and **11,** followed by alkylation of **10** with **11** to give the key intermediate **13.**

Scheme I. Key Intermediates



Synthesis of the *p*-Nitrobenzenesulfonate Esters 11a and 11b. Piperonal is converted to 6-chloro-3,4-methylenedioxyphenylacetic acid in 55% overall yield via the intermediates **14–18** using minor modifications of known procedures.[18–20] Reduction of **17** with lithium aluminum hydride gives an alcohol (**18**) which is converted to *p*-nitrobenzenesulfonate ester **11b** by way of the sodium alkoxide of **18** (from sodium hydride) and a twofold excess of *p*-nitrobenzenesulfonyl chloride. The yellow crystalline sulfonate ester **11b** is obtained in 91% yield from **17,** 49–51% overall yield from piperonal.

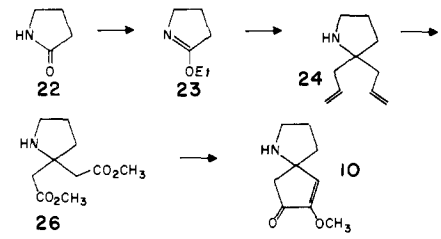


14, R = CH_2OH; X = Cl
15, R = CH_2Cl; X = Cl
16, R = CH_2CN; X = Cl
17, R = CH_2CO_2H; X = Cl
18, R = CH_2CH_2OH; X = Cl
19, R = CH_2CO_2H; X = H
20, R = CH_2CH_2OH; X = H
21, R = CH_2CH_2OH; X = I

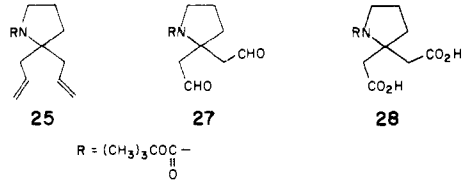
A related sequence produces the iodo analog **11a,** using 3,4-methylenedioxyphenylacetic acid (**19**) from commercial sources. Without purification of intermediates, **19** is reduced to alcohol **20,**[21] iodinated with iodine and silver trifluoroacetate to give the iodo alcohol **21,** and treated with *p*-nitrobenzenesulfonyl chloride and excess pyridine in ether. The resulting *p*-nitrobenzenesulfonate ester **11a** is isolated in 45–55% overall yield after crystallization from carbon tetrachloride. The success of the conversion **21** → **11a** depends on the precipitation of **11a** as it forms in the ether solution, in order to avoid spontaneous displacement of the *p*-nitrobenzenesulfonate unit by chloride ion.

Synthesis of 1-Aza-8-methoxyspiro[4.4]non-8-en-7-one (10). The preparation of **10** involves elaboration of pyrrolidinone (**22**), as outlined in Scheme II. The imidate ester **23** is obtained by reaction of pyrrolidinone with triethyloxonium fluoroborate (or the corresponding methyl imidate can be obtained using methyl fluorosulfonate). Excess allylmagnesium bromide (3 mol equiv) reacts with **23** to afford 2,2-diallylpyrrolidine (**24**) in 84% yield, according to the method reported by Lukes and Cerny for 2,2-diallylpiperidine.[22] The latent carboxymethyl units in **24** are exposed to give **26**

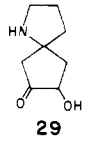
Scheme II. Synthesis of Spirocycle **10**



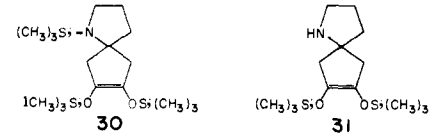
via an ozonolysis sequence which requires protection of the amino group. Reaction of **24** with *tert*-butoxycarbonyl azide[23] provided *N-tert*-butoxycarbonyl-2,2-diallylpyrrolidine (**25**) which can be purified by distillation at reduced pressure but is obtained (>95% yield) directly in sufficient purity for the succeeding steps. The conversion of **25** to **26** requires three operations which are best carried out without isolation of intermediates. Excess ozone in methyl alcohol at −78° followed by excess dimethyl sulfide[24] produces the crude dialdehyde **27** which, with excess silver(I) oxide under basic conditions, is converted to the diacid **28.**[25] Fisher esterification in methyl alcohol produces the dimethyl ester and serves to promote cleavage of the *tert*-butoxycarbonyl group. The amino diester **26** is isolated by distillation, in amounts corresponding to 55–61% overall yield from **24.**



The final stages in the conversion of amino diester **26** to the desired spirocycle **10** involve acyloin-type ring closure of **26** to give **29** or an equivalent, oxidation to the α-diketone **9,** and O-methylation to form **10.** The acyloin ring closure presented unanticipated difficulties. An extensive series of experiments designed to produce **29** by the usual conditions

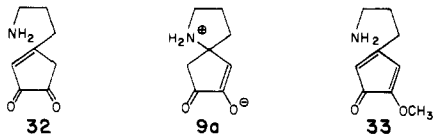


for the acyloin reaction[26] failed in every case to produce characterizable monomeric products. Rühlmann's modification of the acyloin reaction[27] involving chlorotrimethylsilane as coreactant also failed under a variety of conditions: sodium metal in ammonia or toluene at various temperatures, etc. In mysterious contrast, sodium–potassium alloy (Na:K = 1:5) reacted with a mixture of **26** and excess chlorotrimethylsilane in dry benzene at 25° (a mildly exothermic process) to give in high efficiency a product which was tentatively identified as the tris(trimethylsilyl) derivative **30.** The product is unstable and can be hydrolyzed in moist ether at 25° to the bis(trimethylsilyl) ether **31.** Compound



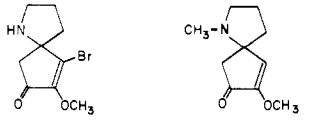
31 also is sensitive to heating (low recovery on distillation) and hydrolysis; the synthetic sequence is most efficiently

continued by direct oxidation of the crude acyloin product (i.e., **30**) via addition of bromine at −78° and spontaneous (ca. −30°) fragmentation to give the α-diketone **9**.[28] Consistent with the cyclopentane-1,2-dione unit, **9** exhibits acidity like that of a carboxylic acid, in this case an amino acid. It polymerizes readily, perhaps via opening of the pyrrolidine ring to give **32,** and is soluble only in more polar solvents (soluble in water and ethyl alcohol, but not in dichloromethane) probably reflecting the zwitterionic formulation (**9a**). Diazomethane in dichloromethane reacts with the crude product mixture containing **9** (in ethyl alcohol) to produce the spirocycle **10,** which cannot be stored neat, even at low temperature, perhaps because of elimination to the reactive cyclopentadienone derivative **33.** Compound **10** can be purified with serious loss of material via chromatography or short path distillation, but it is characterized through conversion to the 2,4-dinitrobenzamide, a stable solid.



32 **9a** **33**

Two important side products appear during this sequence, one which can be avoided by proper control of experimental conditions and a second which does not interfere with further steps. The efficient conversion of **30** to **9** requires exactly 1 mol equiv of bromine; excess bromine leads eventually to 1-aza-9-bromo-8-methoxyspiro[4.4]non-8-en-7-one (**34**), presumably from further addition of bromine (and loss of hydrogen bromide) with α-diketone **9**.[29] The O-methylation of **9** invariably leads to a 10:1 mixture of the secondary amine **10** and the corresponding *N*-methyl analog **35**. Diazomethane was the only methylating agent found to give useful quantities of **10,** and preferential formation of **10** over **35** was generally true in less polar solvents. Diazomethane in *N,N*-dimethylformamide produced **35** as the major product, a rare example of N-methylation with diazomethane.

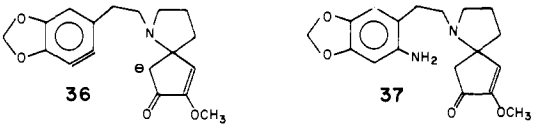


34 **35**

Preparation and Reactions of the Key Intermediates, Halo Ketones 14 and 15. The two legs of the convergent scheme are joined by allowing the crude preparation of **10** to react with the iodosulfonate **11a** in acetonitrile at 25° with excess diisopropylethylamine. The alkylation proceeds smoothly to give crystalline iodo ketone **13a,** which is isolated by column chromatography. The yield of **13a** over the multistep sequence from **26** is 41–51%. In the same way, chlorosulfonate **11b** is used to prepare chloro ketone **13b** in 46% overall yield from **26.**

The ring closure of **13** to cephalotaxinone **6** is the pivotal step in the strategy. With the initial assumption that the most direct route would involve the stabilized anion **12,** attention was focused on methods of activating the appropriate position of the aromatic ring toward coupling with a carbanion. Direct nucleophilic aromatic substitution under mild conditions would clearly require activation of the aromatic ring by electron-withdrawing substituents. But a sequence of attaching and removing such a substituent on the aromatic ring in **13** seemed doomed to inefficiency, and this approach was not pursued.

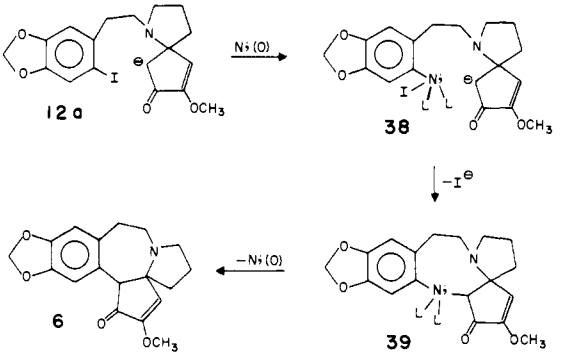
Benzyne Approach.[30] An alternative to nucleophilic aromatic substitution which gives the same overall transformation but does not rely on an electron-deficient aromatic ring is nucleophilic addition to a transient benzyne.[31] In this approach, excess strong base is used to generate the enolate anion and to remove hydrogen halide from the aryl ring which affords the electrophilic benzyne (i.e., **36**). Application of this procedure is successful in converting **13b** to a complex product mixture from which cephalotaxinone (**6**) is isolated in 12–15% yield by repeated preparative layer chromatography. The optimum conditions involve preparation of potassium triphenylmethide (fourfold molar excess) in 1,2-dimethoxyethane[32] and reaction of this solution with chloro ketone **13b** at 30° for 3 hr. Using a sample of natural (−)-cephalotaxinone[33] for orientation during TLC analysis, it was possible to isolate racemic cephalotaxinone from the mixture of at least seven significant products. No other products were characterized, and no evidence was found to suggest the presence of 4-*epi*-cephalotaxinone (**7**). Clearly, the brutal conditions required to promote abstraction of a proton from **12b** are mainly responsible for the significant side reactions; the anion **12b** (lithium salt) is stable for extended periods in tetrahydrofuran at 25°. Other bases (lithium diisopropylamide, potassium hexamethyldisilazide, and potassium *tert*-butoxide) failed to convert **13b** to the benzyne intermediate **36** under mild conditions. Potassium amide in liquid ammonia at reflux gave smooth conversion of **13b** to an aromatic amine which is tentatively identified as **37,** based primarily on similarity of ^{1}H NMR spectral data with **13b,** mass spectral molecular ion, and characteristic ir absorption. The corresponding iodo ketone **13a** was studied under similar conditions with strong base, and no significant quantity of cephalotaxinone was produced.



36 **37**

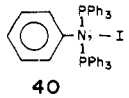
Ring Closure via σ-Arylnickel Intermediates. In order to provide activation of the aryl ring under mild conditions, attention was turned to the oxidative addition of a zerovalent nickel complex to an aryl halide and to the possibilities of intercepting the resulting σ-arylnickel complex with a reactive carbanion, eventually resulting in carbon–carbon coupling. The specific application, outlined in Scheme III, would allow formal nucleophilic aromatic substitution by means of organonickel intermediates (**38** and **39**), where the nickel presumably acts catalytically.[34]

Scheme III. Proposed Pathway for Coupling with Nickel(0)



12a **38** **6** **39**

Many examples are known where zerovalent nickel catalysts such as tetrakis(trialkylphosphine)nickel(0),[35] bis(triphenylphosphine)ethylenenickel(0),[36] and bis(1,5-cyclooctadiene)nickel(0)[37] react directly under mild conditions with aryl halides to form transient[38] or stable[39] σ-arylnickel(II) halide complexes (e.g., **40**). In solution, the σ-aryl ligand is unstable toward coupling to form biaryls, a reaction which forms the basis of a low-temperature analog of the Ullmann reaction.[38a]



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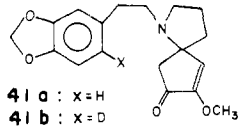
A few examples have been reported where formation of the σ-arylnickel intermediate in the presence of nucleophiles leads to overall replacement of halide by the nucleophile (e.g., cyanide ion[40] and Grignard reagent[41]), although no examples of the more interesting stabilized anions such as an enolate anion (as in **38**) have been reported in reaction with σ-arylnickel complexes.

We observed nucleophilic aromatic substitution by enolate anions on aryl halides at 0° in moderate efficiency using a zerovalent nickel catalyst, where the major limitation was competitive coupling of the aryl units to form biaryl and (catalytically inactive) nickel dihalide.[42] The example of Scheme III appeared more favorable because of the intramolecular nature of the nucleophilic attack and because of inhibition of biaryl formation due to the substantial steric bulk of the side chain on the aryl ring in **12**. In fact, using bis(1,5-cyclooctadiene)nickel(0) as the source of zerovalent nickel in tetrahydrofuran at 25°, the anion **12a** (from **13a** with lithium diisopropylamide) reacts to give a mixture of only two compounds, cephalotaxinone (**6**) and structure **41a** resulting from replacement of iodine with a hydrogen. After preparative layer chromatographic separation, the yield of each product is 30–35%. The source of the hydrogen (X in **41a**) is the solvent (tetrahydrofuran), presumably by hydrogen atom transfer to a σ-arylnickel complex. The same product (**41a**) is the only product when iodo ketone **13a** is allowed to react with zerovalent nickel at 25° in the absence of base; using THF-d_8, the major product is **41b** (82% D by mass spectrometry and ^{1}H NMR). Attempts to favor **6** over **41a** by choosing solvents with lower propensity for hydrogen atom donation (benzene, *N,N*-dimethylformamide, hexamethylphosphoric triamide) failed.[43]

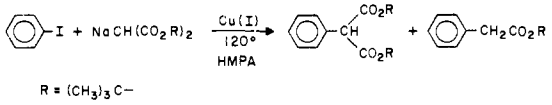


41a : X=H
41b : X=D

Activation of Nucleophilic Aromatic Substitution via Copper(I) Enolates. The high activation barrier involved in direct nucleophilic aromatic substitution by carbanions obviously also appears with heteroatom nucleophiles such as alkoxide, amide, and thiolate anions. It has been known for many years[44] that copper(I) salts of heteroatom nucleophiles react under relatively mild conditions with unactivated aryl halides to give substitution. In anticipation of utilizing the activating effect of cuprous ion for the ring closure **12** → **6**, we considered simple intermolecular examples of copper(I)-activated carbanion coupling with aryl halides.

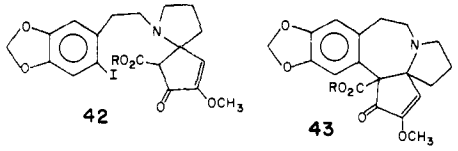
When copper(I) iodide or tri-*n*-butylphosphinecopper(I) iodide and iodobenzene are added to a solution of the lithium enolates of acetophenone or *tert*-butyl acetate in tetrahydrofuran or tetrahydrofuran–hexamethylphosphoric triamide, the enolate anion appears to enter into destructive side reactions (including coupling of two units) below 25°, with no evidence for interaction with the aryl halide. Similarly, treatment of **13a** with lithium diisopropylamide at low temperature in tetrahydrofuran followed by addition of 1 mol equiv of copper(I) iodide or tri-*n*-butylphosphinecopper(I) iodide produced a deep-purple homogeneous solution; after 1 hr at 25°, quenching with acid followed by the usual isolation procedures afforded a complex product mixture containing neither the starting iodo ketone (**13a**) nor the desired product, **6**. Lower reaction temperatures led to recovered starting iodo ketone (**13a**).

The copper-promoted nucleophilic substitution is successful using more stable carbanions. For example, di-*tert*-butyl sodiomalonate reacts with iodobenzene in the presence of copper(I) acetate or copper(I) iodide over 24 hr at 120° in hexamethylphosphoric triamide (HMPA) to give a mixture of di-*tert*-butyl phenylmalonate (60–63%) and *tert*-butyl phenylacetate (3–10%). The latter product presumably arises from cleavage of one ester unit followed by decarboxylation. Longer reaction times and higher temperatures tend to favor the cleavage product. In a control experiment, a mixture of di-*tert*-butyl sodiomalonate and iodobenzene was stirred at 145° in HMPA for several days, resulting in recovery of starting materials in high efficiency. With ethyl sodioacetoacetate, iodobenzene, and copper(I) iodide in HMPA, the main product after 24 hr at 115° is ethyl phen-



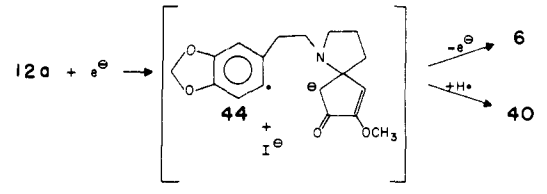
R = $(CH_3)_3C$–

ylacetate (84%), where ketone cleavage has occurred in preference to ester hydrolysis–decarboxylation. In order to apply this method to the preparation of cephalotaxinone, the iodo ketone **13a** was converted to the α-carbethoxy derivative **42** using diethyl carbonate and sodium hydride. However, generation of the corresponding anion in HMPA followed by heating with various copper(I) salts failed to effect the desired ring closure to give **43** (or **6**).



42 43

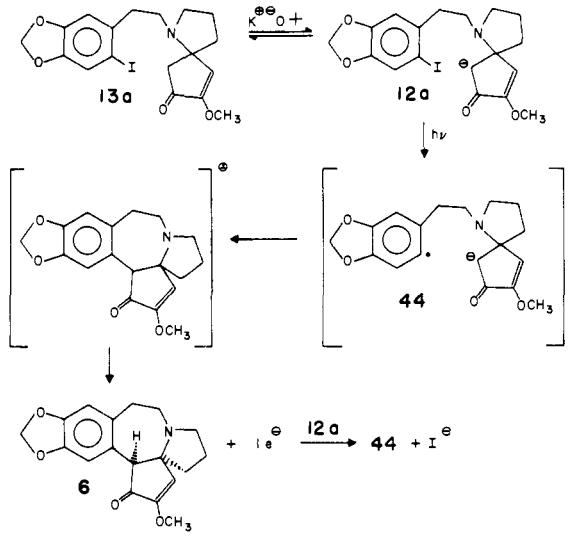
Ring Closure via the SRN1 Reaction. The work of Bunnett and coworkers has established that phenyl radicals are electrophilic species which can couple with nucleophiles, including carbanions.[45-47] A simple technique for generation of the requisite phenyl radicals is alkali metal reduction of heteroatom-substituted aryl rings, such as aryl halides.[46] This general method is successful in simple intermolecular examples such as acetone–enolate coupling with iodobenzene to give deoxybenzoin,[46] providing a low-temperature technique for a process equivalent to nucleophilic aromatic substitution. However, no intramolecular examples had been reported. When iodo ketone **13a** is exposed to potassium amide (1.1 mol equiv) in liquid ammonia at reflux, and then sodium–potassium alloy (1:5, 1.1 mol equiv) is added by microliter syringe, a blue color appears which rapidly changes to yellow. Evaporation of the ammonia and chromatographic separation of the residue afford recovered starting material (35%) and a mixture of cephalotaxinone (29%) and the reduction product **41a** (18%). Based on iodo ketone not recovered, the yield of cephalotaxinone is 45%, but attempts to achieve complete conversion (more Na–K alloy, longer time) lead to lower yields. Other solvents (ether, tetrahydrofuran) tend to favor formation of the reduction product **41a**, presumably because of hydrogen atom transfer to the aryl radical (i.e., **44**) implicated in the radical-chain mechanism suggested for these reactions.[45-47] Quite clearly the vigorous reducing conditions necessary to generate the phenyl radical promote side reactions involving the desired product.



12a + e$^\ominus$ → 44 → 6 (−e$^\ominus$) or 40 (+H•)

Bunnett and Rossi more recently provided an alternative method for generation of phenyl radicals in the presence of anions, employing irradiation to initiate a radical-chain process.[47] In the first intramolecular example, iodo ketone **13a** is suspended (partially soluble) in liquid ammonia at reflux, and 7 mol equiv of solid potassium *tert*-butoxide is added all at once. No change is apparent but, upon external irradiation (Pyrex filter) with a 450-W medium-pressure mercury arc, the solution turned faintly yellow, and the solid dissolved. After 1 hr, irradiation is discontinued, the ammonia is allowed to evaporate, and the residue is purified by preparative layer chromatography. The only detectable product is identified as (+,−)-cephalotaxinone [**6**, 94% yield, mp 180–183° (lit.[8] 170–178°)] by comparison of ^{1}H NMR, ir, and uv spectral data with corresponding data from natural (−)-cephalotaxinone.[33] Using tetrahydrofuran as cosolvent to provide a homogeneous reaction medium, substantial amounts of **41a**, the reduction product, are obtained. The same product appears in significant yield if lower concentration of potassium *tert*-butoxide is used. Since iodo ketone **13a** reacts to give **41a** as the only product upon irradiation in the absence of base, the large excess of potassium *tert*-butoxide used for efficient formation of **6** is probably important in maintaining a high equilibrium concentration of the anion **12a**. The overall pathway expected in analogy with the suggestions of Bunnett and Rossi[47] is detailed in Scheme IV; again, the radical-chain reaction formally requires only a catalytic quantity of photons, but no direct evidence has been collected to support this aspect of the sequence. As anticipated, only the natural C-4 epimer of **6** is observed in the product mixture; the ring closure may be stereospecific or, more likely, equilibration to give the thermodynamically more favorable configuration (i.e., **6**) is rapid under the basic reaction conditions.

Scheme IV. Ring Closure via the Photo-SRN1 Reaction

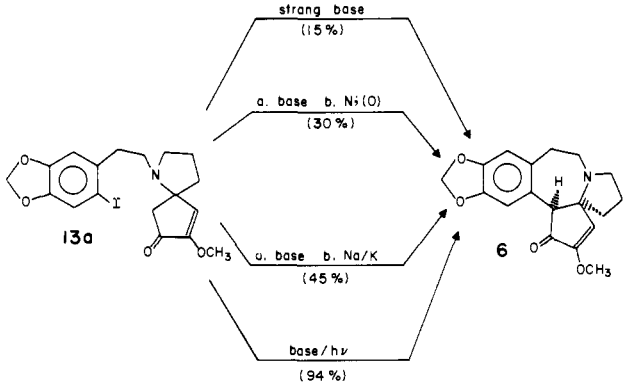


Comparison of the four successful approaches to the critical ring closure, as displayed in Scheme V, reveals the unique efficiency of the photo-stimulated SRN1 reaction.

Cephalotaxine. The final step in the total synthesis of cephalotaxine (**1**) has been developed by others using natural[9] and synthetic[13a] cephalotaxinone. We employed diisobutylaluminum hydride, which produces a single product, (+,−)-cephalotaxine (**1**), isolated in 76% yield and shown to have spectral data superimposable with corresponding data for (−)-cephalotaxinone.[33]

With overall yields in the range of 15% for the conversion of pyrrolidone and 3,4-methylenedioxyphenylacetic acid to the iodo ketone **13a**, the most efficient ring-closure technique (photo-stimulated SRN1) allows synthesis of cephalotaxine in 10% overall yield.

Scheme V



Experimental Section

Apparatus. All ^{1}H NMR spectra were recorded on either a Varian Associates Model A-60A or a Perkin-Elmer R-24 spectrometer. Chemical shifts are expressed in parts per million (δ) downfield from internal tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer Infracord grating spectrophotometer, while uv spectra were obtained with a Cary Model 14 spectrophotometer. Mass spectral data were obtained with an Associated Electrical Industries Model MS-902 spectrometer employing electron-impact ionization unless otherwise specified. Preparative layer chromatography was carried out on 20 × 20 cm glass plates coated with a 1500-μm layer of silica gel G (E. Merck) containing 1% zinc sulfide fluorescent indicator; visualization was with uv light or iodine vapor. GLC was performed on an F & M Model 609 gas chromatograph with flame-ionization detection (analytical) or a Varian Aerograph Model 90-P preparative gas chromatograph equipped with a thermal conductivity detector. Photoreactions were carried out by positioning next to the reaction vessel a photochemical immersion well (Ace 6524-05) containing an Hanovia 450-W medium-pressure mercury arc. All melting points and boiling points are uncorrected unless otherwise noted. The term "under argon" implies that the reaction vessel was alternately evacuated to <20 Torr and filled with argon at least three times.

Reagents. All solvents were ACS reagent grade and were not further purified unless otherwise noted. Dry tetrahydrofuran (THF) was obtained by distillation from sodium benzophenone ketyl under argon immediately before use. Dry benzene was obtained by azeotropic distillation. Hexamethylphosphoric triamide (HMPA) was dried by distillation from phosphorus pentoxide under vacuum. *N,N*-Dimethylformamide (DMF) was purified by distillation from calcium hydride at 50 Torr and stored over activated molecular sieves. All organic extracts were dried over anhydrous magnesium sulfate unless otherwise specified.

2-Chloro-1-hydroxymethyl-4,5-methylenedioxybenzene (14). A suspension of 1.43 g (37.6 mmol) of lithium aluminum hydride in 50 ml of tetrahydrofuran was cooled in an ice bath under argon. A slurry of 13.85 g (75.1 mmol) of 2-chloro-4,5-methylenedioxybenzaldehyde[18] in 40 ml of tetrahydrofuran was added over 20 min. The reaction mixture was stirred at 25° for 12 hr. It was then cooled to 5°, and 1.43 g of water, 1.43 g of 15% aqueous potassium hydroxide, and 4.29 g of water were added sequentially. The mixture was stirred until the solid turned white (ca. 10 min) and was then filtered. The solid was washed with THF, and the filtrate was evaporated under aspirator vacuum. The residue was taken up in chloroform and dried, and the solvent was removed under vacuum to leave 13.5 g (9) of colorless oil. Recrystallization from ethyl alcohol gave a sample: mp 73–74° (lit.[18] 73–74°); ^{1}H NMR ($CDCl_3$) 6.87 (1 H, s), 6.78 (1 H, s), 5.93 (2 H, s), 4.58 (2 H, s), 2.70 (1 H, s).

2-Chloro-1-chloromethyl-4,5-methylenedioxybenzene (15). A solution of 13.5 g (72.4 mmol) of 2-chloro-1-hydroxymethyl-4,5-methylenedioxybenzene (**14**) and 50 ml of thionyl chloride (freshly distilled) in 200 ml of dichloromethane was heated under reflux for 30 min. The volatile materials were removed by rotary evaporation to afford a solid residue, 14.8 g. Distillation through a 10-cm Vigreux column afforded a center cut of bp 64° (0.5 Torr), 12.6 g,

87% yield. The sample solidified: mp 63–64.5° (lit.[18] 65°); ^{1}H NMR ($CDCl_3$) 6.88 (1 H, s), 6.82 (1 H, s), 5.94 (2 H, s), 4.60 (2 H, s).

2-Chloro-1-cyanomethyl-4,5-methylenedioxybenzene (16). A mixture of 14.7 g (71.7 mmol) of 2-chloro-1-chloromethyl-4,5-methylenedioxybenzene (**15**), 7.04 g (143 mmol) of sodium cyanide, and 21 ml of dimethyl sulfoxide was stirred at 25° for 13 hr. The reaction mixture was partitioned between water and ether, and the aqueous layer was washed twice with ether. The combined ether extracts were washed three times with dilute aqueous sodium chloride solution and once with saturated aqueous sodium chloride solution, dried, and concentrated by rotary evaporation to leave a yellow oil, 12.7 g, 91% yield of essentially pure **16**: ^{1}H NMR ($CDCl_3$) 6.94 (1 H, s), 6.84 (1 H, s), 5.99 (2 H, s), 3.72 (2 H, s). Recrystallization from ethyl alcohol gave colorless plates, mp 70–71° (lit.[18] mp 70–71°).

2-Chloro-4,5-methylenedioxyphenylacetic Acid (17). A solution of 12.5 g (190 mmol) of potassium hydroxide (85%) in 125 ml of water was added all at once to a mixture of 12.3 g (63 mmol) of 2-chloro-1-cyanomethyl-4,5-methylenedioxybenzene (**16**) in 40 ml of ethyl alcohol under argon, and the resulting solution was heated at reflux for 8 hr. The reaction mixture was then cooled and poured into cold water, and the aqueous suspension was washed three times with chloroform. Ice was added to the aqueous solution, and the pH was brought to 2 with concentrated hydrochloric acid. The mixture was filtered, and the filtrate was washed three times with ether. The ether solution was dried and concentrated by rotary evaporation to yield a solid residue which was combined with the residue from filtration to give a total of 11.8 g (87%) of crude product. Crystallization from ethyl alcohol–chloroform gave 8.5 g (63%) of colorless crystals, mp 176.5–177° (lit.[18] mp 174–175°). The sequence 6-chloropiperonal → **17** was carried out without isolation of intermediates to afford pure **17** in 55% overall yield: ^{1}H NMR ($CDCl_3$) 12.3–10.8 (1 H, broad s), 6.84 (2 H, s), 5.96 (2 H, s), 3.64 (2 H, s).

2-(2-Chloro-4,5-methylenedioxyphenyl)ethyl Alcohol (18). A solution of 2.87 g (1.34 mmol) of 2-chloro-4,5-methylenedioxyphenylacetic acid (**17**) in 40 ml of dry THF was added slowly to an ice-cold stirred mixture of 532 mg (14 mmol) of lithium aluminum hydride in 15 ml of THF. After addition was complete, the reaction mixture was stirred at 25° for 17 hr. It was then cooled to 0°, and the following solutions were added sequentially over 15 min: 0.5 ml of water, 0.5 ml of 15% aqueous potassium hydroxide solution, and 1.6 ml of water. The resulting mixture was stirred at 25° until the precipitate was white, and then it was filtered. The filtrate was dried and concentrated by rotary evaporation to leave a colorless solid residue, 2.58 g (96% yield of **18**):[48] ^{1}H NMR ($CDCl_3$) 6.79 (1 H, s), 6.69 (1 H, s), 5.90 (2 H, s), 3.82 (2 H, t, J = 6.5 Hz), 2.91 (2 H, t, J = 6.5 Hz), 1.67 (1 H, s). This material was used directly for preparation of **11b**.

2-(2-Chloro-4,5-methylenedioxyphenyl)ethyl Alcohol *p*-Nitrobenzenesulfonate Ester (11b). Alcohol **18** (2.00 g, 10 mmol) and sodium hydride (1.05 g of a 54% slurry in mineral oil, 22.8 mmol) were mixed in 30 ml of dry THF and heated at reflux for 15 hr. Then the mixture was cooled to −78° (drying tube in place), and a solution of *p*-nitrobenzenesulfonyl chloride (4.66 g, 21.0 mmol) in 10 ml of dry THF was added rapidly. The mixture was allowed to warm to 25° and to stir at this temperature for 3 hr. The mixture was partitioned between dichloromethane and cold 5% aqueous hydrochloric acid solution, and the organic layer was then washed sequentially with water and 5% aqueous sodium bicarbonate solution. After being dried, the organic extract was concentrated to afford a yellow solid residue. Crystallization from chloroform–carbon tetrachloride afforded yellow needles, 3.202 g (91% yield): mp 143–144°; ^{1}H NMR ($CDCl_3$) 8.28 (2 H, d, J = 8.5 Hz), 7.80 (2 H, d, J = 8.5 Hz), 6.66 (1 H, s), 6.51 (1 H, s), 5.90 (2 H, s), 4.35 (2 H, t, J = 6.5 Hz), 7.02 (2 H, t, J = 6.5 Hz).

Anal. Calcd for $C_{15}H_{12}NO_7SCl$: C, 46.70; H, 3.14; N, 3.63; Cl, 9.45. Found: C, 46.82; H, 3.00; N, 3.60; Cl, 9.45.

2-(3,4-Methylenedioxyphenyl)ethyl Alcohol (20). To a vigorously stirred suspension of lithium aluminum hydride (13.0 g, 0.133 mol) in anhydrous ether (500 ml) at 25° was added solid 3,4-methylenedioxyphenylacetic acid (**19**, Pfaltz and Bauer, 20.0 g, 0.111 mol) in small portions. After 1.5 hr, the reaction was quenched by sequential addition of water (13 ml), aqueous sodium hydroxide (15%, 13 ml), and water (39 ml). The resulting white suspension was filtered through anhydrous magnesium sulfate, and the filtrate was concentrated by rotary evaporation to give 2-(3,4-methylenedioxyphenyl)ethyl alcohol (**20**), >95% pure by spectral analysis, as a colorless oil (96% yield, 17.6 g): ^{1}H NMR ($CDCl_3$) 2.10 (s, 1 H, –OH), 2.74 (t, 2 H, $ArCH_2$, J = 7 Hz), 3.73 (t, 2 H, $-CH_2O$, J = 7 Hz), 5.83 (s, 2 H, OCH_2O), 6.65 (s, 3 H, ArH). The crude material was used in subsequent experiments without further purification. For an alternative preparation and characterization, see ref 21.

2-(2-Iodo-4,5-methylenedioxyphenyl)ethyl Alcohol (21). To a vigorously stirred suspension of silver trifluoroacetate[49] (33.7 g, 0.153 mol) in chloroform (250 ml) containing 2-(3,4-methylenedioxyphenyl)ethanol (**20**, crude product, 17.85 g, 0.107 mol) was added solid iodine (44.5 g, 0.350 mol) in small portions such that a red color was maintained. After the iodine addition was complete, the suspension of yellow solid was stirred for 1 hr at 25°, then filtered, and the filtrate was washed with 20% aqueous sodium thiosulfate. The organic layer was dried and concentrated by rotary evaporation, and the resulting brown residue was taken up in hot carbon tetrachloride, treated with activated charcoal, filtered, and cooled to cause deposition of colorless crystals (55% yield, 16.72 g): mp 68–69.5°; ^{1}H NMR ($CDCl_3$) 1.98 (s, 1 H, –OH), 3.06 (t, 3 H, $ArCH_2$, J = Hz), 3.68 (t, 2 H, CH_2O, J = 7 Hz), 5.99 (s, 2 H, OCH_2O), 6.81 (s, 1 H, ArH), 7.27 (s, 1 H, ArH).

2-(2-Iodo-4,5-methylenedioxyphenyl)ethyl *p*-Nitrobenzenesulfonate. Pyridine (Fisher, dried over KOH, 0.6 ml) was added to a solution of 2-(2-iodo-3,4-methylenedioxyphenyl)ethyl alcohol (**21**, 1.00 g, 3.42 mmol) and *p*-nitrobenzenesulfonyl chloride (830 mg, 3.76 mmol, 1 excess) in a minimal amount of anhydrous ether (ca. 15 ml). After 13 hr at 25°, two sets of crystals had appeared, one colorless and one yellow. The supernatant liquid was decanted and allowed to stand for further deposition of crystals. After 15 hr, the additional crystals were collected by decantation, and the combined solid product was partitioned between dichloromethane (50 ml) and water (25 ml). The organic layer was washed with ice-cold hydrochloric acid (5%, 25 ml), dried, filtered, and concentrated by rotary evaporation to give a yellow residue. Recrystallization (CCl_4) afforded the iodo nosylate **11a** as yellow crystals (80% yield, 1.405 g), mp 126.5–127.0°. The conversion of **19** to **11a** was accomplished without isolation of **20** and **21** in 51% yield: ir ($CHCl_3$) 5.84 (w), 6.20 (w), 6.53 (s), 6.68 (m), 6.82 (m), 7.45 (s), 8.17 (s), 8.45 μ (s); ^{1}H NMR ($CDCl_3$) 3.10 (t, 2 H, CH_2Ar, J = 7 Hz), 4.42 (t, 2 H, CH_2OSO_2, J = 7 Hz), 6.07 (s, 2 H, OCH_2O), 6.79 (s, 1 H, ArH), 7.30 (s, 1 H, ArH), 8.15 (d, 2 H, NO_2ArH, J = 9 Hz), 8.55 (d, 2 H, NO_2ArH, J = 9 Hz); uv (max) (EtOH) 246 nm (log ϵ 4.23), 280 (3.70), 292 (3.74); mass spectral mol wt (calcd, 477) 477.

Anal. Calcd for $C_{15}H_{12}NO_7SI$: C, 37.75; H, 2.54; N, 2.94, S, 6.72; I, 26.59. Found: C, 37.82; H, 2.75; N, 2.88; S, 6.83; I, 26.54.

2-Ethoxypyrroline (23).[50] To a solution of freshly prepared triethyloxonium fluoroborate[51] (ca. 1300 g, 7 mol) in 2 l. of dichloromethane at 0° under a drying tube, with magnetic stirring, was added pyrrolidinone (reagent grade or redistilled technical grade, 700 ml, 765 g, 9.00 mol) dropwise via an addition funnel. Addition was complete in 1 hr, and the mixture was allowed to stir gently for 12–20 hr at 25°. The contents of the flask was then added cautiously to 1 l. of cold saturated aqueous sodium carbonate solution. The mixture was stirred vigorously, and the organic layer was washed with saturated aqueous sodium carbonate, dried, and fractionated with a 1-m Vigreux column. After the dichloromethane was removed at 760 Torr, the pressure was reduced to 85 Torr, and 2-ethoxypyrroline was obtained [bp 85° (85 Torr), 578 g, 73% yield based on triethyloxonium fluoroborate].

2,2-Diallylpyrrolidine (24). Using the general method of Lukes and Cerny,[22] to a suspension under nitrogen of 400 g (16.5 mol) of magnesium turnings, 3 l. of anhydrous ether, and 0.5 g of iodine crystals in a 12-l. three-necked flask bearing an overhead stirrer and reflux condenser, and cooled in a water bath, was added a solution of 1870 g (15.4 mol) of allyl bromide in 3 l. of anhydrous ether. About 200 ml was added all at once at first to initiate the reaction. The remainder was added dropwise with cooling (ice as needed) to maintain gentle reflux. When the addition was complete (ca. 1 hr), the reaction mixture was allowed to stir for 1 hr at 25°. The mixture was cooled in an ice bath, and, with rapid stirring, a solution of 2-ethoxypyrroline (500 g, 5.05 mol) in 1 l. of anhydrous ether was added dropwise. When about half of the solu-

tion was added, a precipitate began to appear. Addition was complete in 1 hr; the mixture was then heated at gentle reflux for 12–20 hr. To the cooled suspension was added 2 l. of water cautiously to destroy the excess Grignard reagent (evolution of propylene). The suspension was then transferred to a large beaker, and an overhead stirrer was positioned to provide vigorous stirring of the mixture. Barium hydroxide (2 kg) was added, and the solution was stirred to dissolve it. The layers were allowed to separate (relatively clear yellow ether layer and suspension below); the ether layer was collected. Then three additional 1-l. portions of ether were added to the beaker, stirred vigorously, and similarly decanted. The combined ether layers were washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated at aspirator pressure. The residue was fractionally distilled to yield a center cut: bp 75–80° (10 Torr), 592 g, 78%; ir (neat) 3.00 (w), 3.26 (w), 3.40 (m), 6.12 (m), 7.00 (m), 10.05 (m), 10.95 (s); ^{1}H NMR ($CDCl_3$) 6.71–5.53 (2 H, mult), 5.17–4.80 (4 H, complex pattern including a large singlet at 4.88), 3.02–2.74 (2 H, broad t, J = 6.5 Hz), 2.12 (4 H, d, J = 7 Hz), 1.96–1.40 (4 H, complex mult), 1.20 (1 H, broad s); mass spectral mol wt (calcd, 151) 151.

Anal. Calcd for $C_{10}H_{17}N$: C, 79.39; H, 11.34. Found: C, 79.01; H, 11.48.

1-*tert*-Butoxycarbonyl-2,2-di(3-propenyl)pyrrolidine (25). According to a general procedure,[23] a mixture of 2,2-diallylpyrrolidine (**24**, 32 g, 0.212 mol), *tert*-butoxycarbonyl azide (61 g, 0.43 mol), powdered magnesium oxide (17 g, 0.43 mol), water (214 ml), and THF (214 ml) was stirred and heated to 45–55° for 24 hr. The reaction mixture was partitioned between water and ether, and the aqueous phase was washed once with ether. The combined organic solutions were washed with cold 3% aqueous hydrochloric acid solution and then with dilute aqueous sodium bicarbonate solution, dried, and concentrated by rotary evaporation. The residue was essentially pure 1-*tert*-butoxycarbonyl-2,2-di(3-propenyl)pyrrolidine (**25**, 53 g, 100% yield). Fractional distillation through a 30-cm Vigreux column afforded a center cut: bp 70–72° (0.1 Torr), 46.5 g, 88% yield; ir (neat) 3.30 (m), 5.93 (s), 6.15 (w), 7.24 (s), 8.50 (s), 10.0 (m), 10.9 μ (m); ^{1}H NMR ($CDCl_3$) 6.12–5.30 (2 H, complex mult), 5.26–4.83 (4 H, complex mult), 3.34 (2 H, broad t, J = 6.5 Hz), 2.85 (2 H, d of d, J_{AX} = 14, J_{BX} = 6 Hz), 2.25 (2 H, d of d, J_{AX} = 14, J_{BX} = 7 Hz), 1.92–1.38 (13 H, complex unit overlapping a singlet at 1.44); mass spectral mol wt (calcd, 251) 251.

Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.65; H, 10.03; N, 5.58. Found: C, 71.35; H, 9.98; N, 5.59.

Conversion of 25 to Dimethyl-2,2-di(carboxymethyl)pyrrolidine (26). Ozone (ca. 2% in oxygen) was introduced into a solution of 1-*tert*-butoxycarbonyl-2,2-di(3-propenyl)pyrrolidine (**25**, 10.3 g, 41.0 mmol) in 180 ml of methyl alcohol at −78° until the blue color persisted for more than 2 min. The excess ozone was removed by allowing oxygen to bubble through the solution at −78°. Then excess (9 ml) of dimethyl sulfide was added rapidly, the mixture was allowed to warm to 25° over 30 min, and the volatile material was removed by rotary evaporation at 25°. The colorless residue was taken up in 1:1 dioxane:water (100 ml) and stirred with solid silver oxide (from 45 g of silver nitrate),[52] and a 13% solution of potassium hydroxide in water was added dropwise until the mixture remained basic (pH 14). A silver mirror appeared on the surface of the vessel. The suspension was filtered through Celite, and the filtrate was made acidic (pH <2) with concentrated hydrochloric acid. The water was removed at reduced pressure (20 Torr) and 50°. The brown solid residue was dried by evacuation to 0.01 Torr for 15 hr or by azeotropic distillation with benzene at 760 Torr. A suspension of the dry solid in 300 ml of acidic methyl alcohol (prepared by adding sufficient acetyl chloride to methyl alcohol to give 6% solution of hydrogen chloride) containing 20 ml of triethyl orthoformate was heated at reflux for 20–25 hr, cooled, and poured into 100 ml of ice-cold saturated aqueous sodium carbonate solution. The resulting mixture was filtered, and sufficient solid sodium hydroxide was added to bring the pH above 12. Extraction with five 100-ml portions of dichloromethane followed by drying and concentrating of the combined extracts afforded 7.2 g of brown oil. Simple distillation produced a single fraction: bp 74–76° (0.01 Torr), 5.4 g, 61% yield; ir (neat) 3.40 (m), 5.77 μ (s); ^{1}H NMR ($CDCl_3$) 1.7–2.0 (m, 4 H, CH_2CH_2, in pyrrolidine ring), 2.38 (s, 1 H, NH), 2.70 (s, 4 H, CH_2CO), 2.9–3.2 (m, 2 H, CH_2N), 3.72 (s, 6 H, CO_2CH_3); mass spectral mol wt (calcd, 215) 215.

Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.78; H, 7.97; N, 6.51. Found: C, 55.53; H, 8.10; N, 6.56.

1-Aza-8-methoxyspiro[4.4]non-8-en-7-one (10). Excess sodium–potassium alloy (1:5, 4.4 ml)[53] and chlorotrimethylsilane (Aldrich, freshly distilled, 6.4 ml, 7.48 g, 70.9 mmol) were added sequentially to a stirred 100-ml portion of dry benzene at 25° (water bath) under argon. Dimethyl-3,3-di(carboxymethyl)pyrrolidine (**26**, 2.0 ml, 2.15 g, 10.0 mmol) was added all at once and, after an induction period of a few minutes, a mildly exothermic reaction began. After 10–15 hr at 25°, the suspension was filtered through Celite using argon pressure. The filtrate was concentrated by rotary evaporation to leave a colorless oil which was dissolved in dichloromethane (50 ml, dried over magnesium sulfate). To this stirred solution at −78° under argon was added a solution of bromine (0.5 ml, 1.56 g, 9.75 mmol) in dichloromethane over 15–20 min, producing a pale-orange solution. The cold solution was allowed to warm to 25° or, more simply, transferred directly to the rotary evaporator and concentrated while warming slowly to 25° (20–30 min) to leave a brown solid.

At the same time, a solution of diazomethane in methylene chloride was prepared as follows.[54] Solid *N*-methyl-*N*-nitrosourea (Pfaltz and Bauer, 12.0 g, 116 mmol) was added in small portions to a cooled (ice), stirred, two-phase system of dichloromethane (200 ml) and aqueous potassium hydroxide solution (6%, 200 ml). After the solid disappeared, the aqueous layer was decanted, and the yellow dichloromethane layer was poured into an addition funnel equipped with a Teflon stopcock.

This solution of diazomethane was added dropwise to a solution in ethyl alcohol at 0° of the brown solid product from bromination. After addition was complete (15 min), the solution was allowed to warm to 25° under aspirator vacuum to remove excess diazomethane. Concentration by rotary evaporation afforded a brown oil which was triturated with ether to give a solution containing mainly the azaspirocycle **10**, and the *N*-methyl analog **35**, and small amounts of polymeric material. A ratio of 10:1 of **10**:**35** was ascertained by integration of the vinyl proton ^{1}H NMR signals. The yield of **10** in the mixture was shown to be 63–66% by quantitative ^{1}H NMR integration. Column chromatography (neutral alumina, Woelm Activity IV) eluting with dichloromethane allowed isolation of a purified sample of **10** (45–55% yield) and of **35**.

Compound **10**: ir (neat) 3.00 (broad, m), 5.80 (s), 6.12 μ (s); ^{1}H NMR ($CDCl_3$) 1.7–2.0 (m, 4 H, CH_2CH_2 in pyrrolidine ring), 2.30 (s, 1 H, NH), 2.46 (s, 2 H, CH_2CO), 2.9–3.2 (m, 2 H, CH_2N), 3.68 (s, 3 H, OCH_3), 6.15 (s, 1 H, vinyl H); mass spectral mol wt (calcd, 167) 167. Reaction with 3,5-dinitrobenzoyl chloride produced the 3,5-dinitrobenzamide of **10**, mp 236.5–237° (benzene).

Anal. Calcd for 3,5-dinitrobenzamide derivative $C_{16}H_{15}O_7N_3$: C, 53.18; H, 4.19; N, 11.64. Found: C, 53.13; H, 3.99; N, 11.15.

Compound **35**: ir (neat) 5.80 (s), 6.12 μ (s); ^{1}H NMR ($CDCl_3$) 1.7–2.0 (m, 4 H, CH_2CH_2 in pyrrolidine ring), 2.19 (s, 3 H, NCH_3), 2.24 (s, 1 H, NH), 2.53 (center of AB q, CH_2CO, $J \sim 15$ Hz), 2.9–3.2 (m, 2 H, CH_2N), 3.76 (s, 3 H, OCH_3), 6.04 (s, 1 H, vinyl H); mass spectral mol wt (calcd, 181) 181.

Intermediates in the Conversion of 26 to 10. In separate experiments, the conversion of **26** to **10** was interrupted in order to characterize (partially) the intermediates **30**, **31**, and **9**, and the by-product, **34**. Under exactly the conditions above for the reaction of sodium–potassium alloy with the amino diester **26** and chlorotrimethylsilane, the crude product (**30**) was examined by ^{1}H NMR spectroscopy and mass spectrometry: ^{1}H NMR ($CDCl_3$) 0.12 (s, 27 H, $SiCH_3$), 1.5–1.9 (m, 4 H, CH_2CH_2 in pyrrolidine ring), 2.21 (broad d, 2 H, one H from each $CH_2C{=}C$, J = 16 Hz), 2.48 (broad d, 2 H, one H from each $CH_2C{=}C$, J = 16 Hz), 2.95 (broad t, 2 H, CH_2N, J = 7 Hz); mass spectral mol wt (calcd, 371) 371.

Attempted distillation [short path, <100° (0.01 Torr)] or hydrolysis in moist ether converted **30** to **31**: ^{1}H NMR ($CDCl_3$) 0.12 (s, 18 H, $SiCH_3$), 1.42–1.80 (m, 4 H, CH_2CH_2 in pyrrolidine ring), 1.60 (s, 1 H, NH), 2.20 (s, 4 H, $CH_2C{=}C$), 2.90 (broad t, 2 H, CH_2N, $J \sim 6$ Hz); mass spectral mol wt (calcd, 299) 299.

Addition of 1 mol equiv of bromine to a solution of **31** in dichloromethane at −78° gave a yellow solution which was allowed to

warm to 25° over 30 min. A solid formed which was collected and dried. The yield of tan, hygroscopic, amorphous solid was approximately quantitative. It was insoluble in acetone, THF, and ether: ^{1}H NMR (DMSO-d_6) 1.87–2.27 (m, 4 H, CH_2CH_2 in pyrrolidine ring), 2.51 (d, 1 H, one H in CH_2CO, J = 19 Hz), 2.94 (d, 1 H, one H in CH_2CO, J = 19 Hz), 3.30 (m, 2 H, CH_2N^+), 6.48 (s, 1 H, vinyl H in zwitterion structure **9a**), 0.63 (broad s, 2 H, H_2N^+).

In an experiment where excess bromine was added (inadvertently) during bromination of **30** or **31**, a new product (**34**) appeared after methylation with diazomethane. Using exactly 2 mol equiv of bromine, **34** was the major product, isolated by preparative layer chromatography in 44% yield: ^{1}H NMR ($CDCl_3$) 1.87–2.24 (m, 4 H, CH_2CH_2 in pyrrolidine ring), 2.10 (s, 1 H, NH), 2.48 (s, 2 H, CH_2CO), 2.9–3.2 (m, 2 H, CH_2N), 4.01 (s, 3 H, OCH_3); mass spectral mol wt (calcd, 245 and 247) 245 and 247 (bromine isotope pattern).

1-Aza-1-[(2-chloro-4,5-methylenedioxyphenyl)ethyl]-8-methoxyspiro[4.4]non-8-en-7-one (13b). A solution of 350 mg (0.907 mmol) of chloro nosylate **11b**, 322 mg (2.50 mmol) of diisopropylethylamine (freshly filtered through Woelm basic alumina I), and 230 mg (1.2 mmol) of crude azaspirocycle **10** in 3 ml of acetonitrile was heated to 55° for 19 hr. The reaction mixture was partitioned between dilute aqueous potassium hydroxide solution and dichloromethane. The aqueous layer was washed twice with dichloromethane, and the combined organic extracts were washed with dilute aqueous hydrochloric acid (the ammonium salt of **13b** remains in the dichloromethane solution), and then with dilute base again. After the dichloromethane solution was dried and concentrated, the residue was introduced onto a column of alumina (Woelm, Activity I). Unreacted chloro nosylate **11b** was eluted with benzene and 5% ethyl acetate–benzene. Elution with 50% ethyl acetate–benzene yielded 273 mg (88% yield) of colorless crystalline solid; one recrystallization from benzene–hexane gave **13b** as needles: mp 109.9–110.7°; ir ($CHCl_3$) 5.82 (s), 6.13 μ (s); ^{1}H NMR ($CDCl_3$) 1.8–2.1 (m, 4 H, CH_2CH_2 in pyrrolidine ring), 2.30 (AB qt, 2 H, J = 14 Hz, CH_2CO), 2.5–3.1 (broad m, 6 H, CH_2NCH_2, $ArCH_2$), 3.67 (s, 3 H, CH_3O), 5.88 (s, 2 H, OCH_2O), 5.92 (s, 1 H, C=CH), 6.61 (s, 1 H, aryl H), 6.72 (s, 1 H, aryl H); mass spectral mol wt (calcd for $C_{18}H_{20}NO_4{}^{35}Cl$, 349) 349.

Anal. Calcd for $C_{18}H_{20}NO_4Cl$: C, 61.80; H, 5.76; N, 4.00; Cl, 10.13. Found: C, 61.77; H, 5.68; N, 3.96; Cl, 10.32.

1-Aza-1-(2-iodo-4,5-methylenedioxyphenyl)ethyl-8-methoxyspiro[4.4]non-8-en-7-one (13a). The 1-aza-8-methoxyspiro[4.4]non-8-en-7-one (**10**, crude product after trituration as described above, from 5.0 mmol of amino diester **25**, ca. 3.5 mmol of **10**) was dissolved in acetonitrile (Eastman Spectroquality, stored over activated molecular sieves, 16 ml) containing 2-(2-iodo-4,5-methylenedioxyphenyl)ethyl *p*-nitrobenzenesulfonate (**11a**, 3.075 g, 6.5 mmol) and diisopropylethylamine (Aldrich, dried by filtration through Woelm alumina I neutral, 6.0 ml). After being stirred at 25° for 76 hr, the mixture was poured into cold dichloromethane (50 ml) which was then washed sequentially with cold 5% aqueous hydrochloric acid (40 ml; the hydrochloride salt of the expected product **13a** remains in the dichloromethane solution) and cold 15% aqueous potassium hydroxide (40 ml). The dichloromethane solution was dried and concentrated by rotary evaporation to a brown semisolid. Chromatography on 100 g of alumina (Woelm Activity III neutral, packed in *n*-pentane) provided a small amount of unreacted iodo nosylate **11a** (eluted with 1:1 *n*-pentane:dichloromethane) followed by the desired iodo ketone **13a** (eluted with dichloromethane). The progress is conveniently followed by TLC (silica gel, eluted with ethyl acetate) where **11a** appeared at R_f 0.80 and **13a** appeared at R_f 0.25. The yield of **13a** is 1.123 g, 51% overall from **26**, 70% based on amount of **10** present according to quantitative ^{1}H NMR analysis. After recrystallization (ether), the mp was 119–119.5°: ir ($CHCl_3$) 5.81 (s), 6.14 (m), 6.79 (m), 8.18 (m), 8.96 (w), 9.61 (m), 11.98 μ (m); ^{1}H NMR ($CDCl_3$) 1.80–2.10 (m, 4 H, CH_2CH_2 in pyrrolidine ring), 2.3 (AB q, 2 H, CH_2CO, J = 14 Hz), 2.6–3.2 (m, 6 H, CH_2NCH_2 and CH_2Ar), 3.70 (s, 3 H, OCH_3), 5.98 (s, 2 H, OCH_2O), 6.04 (s, 1 H, C=CH), 6.74 (s, 1 H, ArH), 7.24 (s, 1 H, ArH); uv (max) (EtOH) 246 nm (log ϵ H, ArH), 7.24 (s, 1 H, ArH); uv (max) (EtOH) 246 nm (log ϵ 4.23), 280 (3.70), 292 (3.74); mass spectral mol wt (calcd, 441) 441.

Anal. Calcd for $C_{18}H_{20}NO_4I$: C, 49.00; H, 4.57; N, 3.17; I, 28.76. Found: C, 48.83; H, 4.64; N, 3.09; I, 28.76.

(+,−)-Cephalotaxinone (6) by the Benzyne Reaction. Approximately 8 ml of ammonia was condensed under argon, and tiny pieces of potassium metal were added until the initial color persisted. A trace of ferric nitrate was added, followed by 40 mg (1 mmol) of potassium. The solution was gray after 5 min, and 252 mg (1.0 mmol) of triphenylmethane in 3 ml of 1,2-dimethoxyethane was added. The ammonia was allowed to boil off, and the system was evacuated and filled with argon several times. A solution of chloro ketone **13b** (60 mg, 0.172 mmol) in 1.0 ml of 1,2-dimethoxyethane was added all at once at 25°, and the mixture was heated at 30° for 3 hr. The red color changed to clear brown, and the reaction mixture was partitioned between dilute aqueous potassium hydroxide solution and dichloromethane. The aqueous phase was washed with dichloromethane, and the combined organic extracts were dried and concentrated by rotary evaporation. The brown solid residue was subjected to preparative layer chromatography on silica gel, eluting with ethyl acetate. One band (R_f 0.35) yielded 9.0 mg (16%) of a colorless oil which solidified upon evaporation of an ether solution. The TLC, ^{1}H NMR, ir, and mass spectral analytical data on this product were identical with corresponding data supplied[33] on natural (−)-cephalotaxinone or measured on the small sample provided us.[33]

Preparation of 1-Aza-1-(2-amino-4,5-methylenedioxyphenyl)ethyl-8-methoxyspiro[4.4]non-8-en-7-one (37). Potassium amide (1.0 mmol) was prepared as usual from potassium (40.2 mg, 1.0 mmol) in liquid ammonia (8 ml) and a catalytic amount of ferric nitrate, at −33°. A solution of chloro ketone **13b** (60 mg, 0.172 mmol) in 1.0 ml of dry THF was added all at once. After 1 hr at −33°, excess ammonium nitrate was added, and the ammonia was allowed to boil off. The residue was partitioned between dilute aqueous potassium hydroxide and dichloromethane, and the aqueous phase was washed with dichloromethane. The combined dichloromethane extracts were shaken with dilute aqueous hydrochloric acid [the starting chloro ketone **13b** and cephalotaxinone (**6**) would remain in the dichloromethane layer]; the acid layer was made basic with KOH pellets and washed with three portions of dichloromethane. The combined dichloromethane solution was dried and concentrated, and the main component was isolated by preparative layer chromatography. Obtained was 24 mg (40%) of a colorless oil which has been tentatively identified as **37** based on similarity of ^{1}H NMR and ir data compared with **13b** and mass spectral molecular weight: ir ($CHCl_3$) 2.94 (w, NH), 3.00 (w, NH), 3.32 (m), 5.81 (s), 6.13 μ (m); ^{1}H NMR ($CDCl_3$) 1.80–2.10 (m, 4 H, CH_2CH_2 in pyrrolidine ring), 2.21 (center of AB pattern appearing as two peaks separated by 4 Hz, 2 H, CH_2CO), 2.52 (br s, ca. 2 H, NH_2), 2.5–3.4 (br m, ca. 6 H, CH_2NCH_2 and $ArCH_2$), 3.63 (s, 3 H, OCH_3), 5.81 (s, 2 H, OCH_2O), 5.93 (s, 1 H, C=CH), 6.28 (s, 1 H, ArH), 6.50 (s, 1 H, ArH). The absence of spin–spin coupling between the aryl hydrogens as revealed by the ^{1}H NMR spectrum is consistent with the para orientation required in **37**.[55] Mass spectrum (chemical ionization, isobutane): m/e 332 (parent + 2, 1), 331 (parent + 1, 10), 330 (parent, 4%), 317 (5%), 231 (1%), 180 (3%), 119 (4%). High resolution (electron impact): parent at m/e (calcd for $C_{18}H_{22}N_2O_4$, parent at 330.1580) 330.1586.

(+,−)-Cephalotaxinone (6) using Zerovalent Nickel. Lithium triphenylmethylide was prepared under argon by adding methyllithium (0.24 mmol, solution in ether) to a solution of triphenylmethane (133 mg, 0.6 mmol) in dry THF (2 ml) at 25° and allowing the red solution to stir for ca. 3 hr. With the red solution at −78°, a solution of the iodo ketone (**13a**, 106 mg, 0.2 mmol) in dry THF (1 ml) was added dropwise. Bis(1,5-cyclooctadiene)nickel(0)[37] (71 mg, 0.26 mmol) was then added as a solid, and the resulting yellow-orange suspension was allowed to warm to 25°. Within 1 hr, a color change to red-brown took place. After 13.5 hr, water (5 ml) and ether (15 ml) were added, and the suspension was filtered. The aqueous phase of the filtrate was washed twice with ether; the combined organic solutions were washed once with saturated aqueous sodium chloride solution, dried, and concentrated by rotary evaporation. Examination of the ^{1}H NMR spectrum of the residue indicated a simple mixture of two components in addition to triphenylmethane. Preparative layer chromatography (silica gel–20% methyl alcohol in ethyl acetate) failed to separate the components (R_f 0.50 and 0.45) efficiently, but provided a mixture (54 mg) for which analysis of the ^{1}H NMR spectrum allowed demonstration of the presence of cephalotaxinone (**6**, $-OCH_3$ singlet at δ 3.81, 20 ±

2 mg, ca. 28% yield) and the reduction product **41a** (-OCH_3 singlet at δ 3.70, 30 ± 2 mg, ca. 41% yield). Other experiments with modified conditions afforded variable ratios of **6** and **41a**, but the yield of **6** was never substantially higher. Samples of both **6** and **41a** were isolated by repeated preparative layer chromatography and conclusively identified by comparison of TLC, ^{1}H NMR, and ir data with corresponding data for **6** (see above) and for **41a** (see below).

1-Aza-1-[4,5-methylenedioxyphenyl)ethyl-8-methoxyspiro-[4.4]non-8-en-7-one (41a). Exactly according to the procedure used to prepare **13a**, the *p*-nitrobenzenesulfonate ester of 2-(3,4-methylenedioxyphenyl)ethyl alcohol (**20**) was used to alkylate **10**. Column chromatography (Woelm Alumina IV neutral) afforded ketone **41a**, as an oil eluted with dichloromethane, for comparison with the reduction product in the experiment directly above: ir ($CHCl_3$) 3.30 (m), 5.82 (s), 6.14 (w), 6.79 (m), 8.14 μ (m); ^{1}H NMR ($CDCl_3$) 1.80-2.10 (m, 4 H, CH_2CH_2 in pyrrolidine ring), 2.25 (center of AB q appearing as two peaks separated by ca. 6 Hz, 2 H, CH_2CO), 2.50-3.00 (m, 6 H, CH_2NCH_2 and $ArCH_2$), 3.67 (s, 3 H, OCH_3), 5.89 (s, 2 H, OCH_2O), 5.94 (s, 1 H, C=CH), 6.64 (s, 3 H, ArH); mass spectral mol wt (calcd for $C_{18}H_{20}NO_4$, 315) 315.

Reaction of 13a with Nickel(0) in the Absence of Base. The iodo ketone **13a** (50 mg, 0.11 mmol) was dissolved in THF-d_8 (1 ml, Merck, dried over lithium aluminum hydride), containing DMF (0.12 mmol; to minimize decomposition of the nickel reagent to metallic nickel). With the mixture under argon at −78°, bis(1,5-cyclooctadiene)nickel(0) (67 mg, 0.24 mmol) was added as a solid, and the resulting mixture was allowed to warm to 25°. After 15 hr at 25°, water and ether were added. The ether solution was washed with water, dried, and concentrated to give a residue of nearly pure **41a** and/or **41b** (40 mg). Isolation by preparative layer chromatography gave a pure sample, 26 mg, 68% yield. Integration of the multiplet at δ 6.64 (all three aryl H) relative to the singlet at δ 3.67 (OCH_3) indicated the presence of deuterium above natural abundance on the aryl ring. Assuming the deuterium is introduced exclusively at the position bearing iodine in **13a**, the extent of incorporation is 82 ± 10%.

A control experiment using identical conditions but with unlabeled THF produced **41a** with 0 ± 5% deuterium incorporation above natural abundance at the aryl hydrogen positions. Another experiment using identical conditions (unlabeled THF), but with deuterium oxide employed to quench the reaction instead of water, also resulted in reduction product **41a** (61% yield after preparative layer chromatography) with 0 ± 5% deuterium incorporation above natural abundance at the aryl hydrogen positions.

Copper(I)-Promoted Reaction of Sodiomalonate with Iodobenzene. To a stirred suspension of sodium hydride (1.40 g of a 43% suspension in mineral oil, 25 mmol, triturated with anhydrous ether) under argon in 10 ml of HMPA at 25° was added di-*tert*-butyl malonate (5.40 g, 25 mmol) over 10 min. After 10 min at 25°, iodobenzene (5.10 g, 25 mmol) was added all at once, followed by solid copper(I) iodide (4.75 g, 25 mmol). The mixture was heated at 120° for 24 hr, cooled to 25°, and partitioned between ether and 10% aqueous ammonium hydroxide. The ether layer was washed sequentially with aqueous ammonium hydroxide and saturated aqueous sodium chloride solution, dried, and concentrated by rotary evaporation. Short-path distillation afforded two fractions. The first [bp 30-50° (0.05 Torr)] amounted to 0.38 g (8% yield) of essentially pure *tert*-butyl phenylacetate: ^{1}H NMR ($CDCl_3$) 1.40 (s, 9 H, CH_3), 3.58 (s, 2 H, CH_2), 7.34 (s, 5 H, ArH). The second [bp 50-100° (0.05 Torr)] amounted to 4.62 g (63% yield) of essentially pure di-*tert*-butyl phenylmalonate: ^{1}H NMR ($CDCl_3$) 1.41 (s, 18 H, CH_3), 4.58 (s, 1 H, CH), 7.30 (s, 5 H, ArH).

Copper(I)-Promoted Reaction of Sodioacetoacetate with Iodobenzene. Exactly as directly above, a mixture of ethyl acetoacetate (3.25 g, 25 mmol), sodium hydride (25 mmol), iodobenzene (25 mmol), and copper(I) iodide (25 mmol) was heated at 110° for 24 hr. The crude product was distilled (short path) to yield a fraction, bp 40-50° (0.8 Torr), 3.34 g (84% yield) of ethyl phenylacetate: ^{1}H NMR ($CDCl_3$) 1.20 (t, 6 H, J = 7.2 Hz), 4.20 (q, 4 H, J = 7.2 Hz), 3.58 (s, 2 H, CH_2), 7.30 (s, 5 H, ArH).

1-Aza-9-carboethoxy-1-(2-iodo-4,5-methylenedioxyphenyl)ethyl-8-methoxyspiro[4.4]non-8-en-7-one (42). To a suspension of sodium hydride (239 mg of a 57% suspension in mineral oil, washed with pentane, 5.20 mmol of NaH) in diethyl carbonate (Aldrich, freshly distilled, 10 ml) under argon was added iodo ketone **13a** (1.000 g, 2.26 mmol), and the mixture was heated at 90° with stirring. After 6 hr, the mixture was poured into aqueous sodium carbonate solution (20%, 25 ml) and extracted with 5 × 25-ml portions of dichloromethane. The combined extracts were dried and concentrated by rotary evaporation to leave a brown semisolid. Attempts to recrystallize the product were unsuccessful. Material of sufficiently high purity for further experiments was obtained by trituration with ether; this solvent dissolved the main product. Evaporation of the ether provided a tan, amorphous solid, 801 mg, 71% yield: ^{1}H NMR ($CDCl_3$) 1.30 (t, 3 H, CH_3 in OEt, J = 7 Hz), 1.73-2.19 (m, 4 H, CH_2CH_2 in pyrrolidine ring), 2.29-3.05 (m, 6 H, CH_2NCH_2 and $ArCH_2$), 3.35 (s, 1 H, $OCCHCO_2Et$), 3.74 (s, 3 H, -OCH_3), 4.20 (q, 2 H, OCH_2O), 5.98 (s, 1 H, C=CH), 6.71 (s, 1 H, ArH), 7.73 (s, 1 H, ArH); mass spectrum m/e 513 (parent, <0.1%), 467, 442, 426, 274, 254, 206, 180, 164, 148, 135.

Reaction of Keto Ester 42 with Sodium Hydride and Copper(I) Iodide. To a suspension of sodium hydride (8.5 mg of a 57% suspension in mineral oil, 0.19 mmol of NaH) in DMF (1.0 ml) under argon was added keto ester **42** (79 mg, 0.154 mmol). When gas evolution ceased, the solution was filtered under argon into a flask containing copper(I) iodide (35 mg, 0.19 mmol) and then was heated to 110°. After 5 hr, the mixture was cooled and quenched with 0.25 ml of concentrated aqueous ammonium hydroxide. The resulting mixture was poured into dichloromethane and washed repeatedly with aqueous sodium carbonate solution containing ammonium hydroxide (0.25 ml:5 ml) until the washings were colorless. The organic phase was dried and concentrated to afford a pale brown solid. Preparative layer chromatography (silica gel, eluted with ethyl acetate) gave eight separate fractions, none of which corresponded to cephalotaxinone (**6**) or the simple cyclization product, **43**, by spectral analysis.

(+,−)-Cephalotaxine (6) by Reductive SRN1 Reaction. To a solution of sodium-potassium mixed amide (prepared from 7.0 μl. of 1:5 sodium-potassium alloy and liquid ammonia with ferric nitrate catalyst, 0.19 mmol) in ammonia at reflux was added iodo ketone **13a** (65 mg, 0.15 mmol). A white solid appeared during stirring for 45 min, and then sodium-potassium alloy (1:5, 70 μl., 0.19 mmol) was added producing an immediate blue color which rapidly changed to pale yellow. After 30 min, methyl alcohol (5 ml) and aqueous sodium carbonate (10%, 5 ml) were added, and the ammonia was allowed to evaporate. The methanolic solution was diluted with aqueous sodium carbonate and extracted with dichloromethane (4 × 10 ml). The combined extracts were dried, concentrated, and separated by preparative layer chromatography (silica gel, eluted with ethyl acetate) into two fractions, R_f 0.32-0.49 and R_f 0.16-0.32. The first fraction was identified as the starting iodo ketone **13a** (22.7 mg, 35% recovery), while the second fraction was a simple mixture (21.9 mg) of cephalotaxinone (**6**) and the reduction product **41a** (ratio, 62:38, respectively) by ^{1}H NMR spectral analysis. Yields were: **6**, 29%; **40**, 18%. Based on **13a** not recovered, they were: **6**, 45%; **41a**, 28%.

(+,−)-Cephalotaxinone (6) by Photostimulated SRN1 Reaction. To a solution of excess potassium *tert*-butoxide (sublimed, 210 mg, 1.87 mmol) in ammonia (15 ml, dried by condensation over sodium and distillation into the reaction vessel) under argon was added solid iodo ketone **13a** (117 mg, 0.267 mmol). The colorless suspension was irradiated externally with a Hanovia 450-W medium-pressure mercury arc (Pyrex filter) for 1 hr to produce a yellow solution. Quenching with sodium carbonate in a water-methyl alcohol solution gave a colorless solution. After the ammonia had evaporated, the residual mixture was partitioned between water and ether. From the ether solution, after drying, concentrating, and purifying by preparative layer chromatography (silica gel, ethyl acetate), was isolated a band of R_f 0.15-0.45 (only detectable product) which was identified as (+,−)-cephalotaxinone (**6**, 79 mg, 94% yield), mp 180-183° (lit.[8] 170-178° dec). Ir and ^{1}H NMR spectra are superimposable with those of natural (−)-cephalotaxine.[33] High-resolution mass spectral mol wt (calcd for $C_{18}H_{19}NO_4$, 313.1314) 313.1296. Uv (max) (EtOH) 291 nm (log ϵ 3.44), 243 (3.75).

(+,−)-Cephalotaxine (1). To a solution of (+,−)-cephalotaxinone (**6**, 14 mg, 0.045 mmol) in dry THF (5 ml) at 0° under argon was added diisobutylaluminum hydride (Ventron, 0.93 M in hexane, 0.133 ml, 0.121 mmol) dropwise over 5 min. After stirring for 3.25

hr, the reaction was quenched with methyl alcohol (2 ml), filtered, and concentrated by rotary evaporation to leave a pale-yellow oil. Traces of solvent were removed at 0.01 Torr, affording (+,−)-cephalotaxine (**1**) as an amorphous solid, 10 mg, 74% yield. Infrared, ^{1}H NMR, and mass spectral data for this material are superimposable with corresponding data of natural (−)-cephalotaxine.[33]

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References and Notes

(1) Alfred P. Sloan Foundation Fellow, 1973–1975; recipient of a Camille and Henry Dreyfus Teacher-Scholar Grant, 1973–1978.
(2) National Institutes of Health Postdoctoral Trainee.
(3) National Institutes of Health Graduate Trainee.
(4) National Science Foundation Undergraduate Research Participant.
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